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Worldwide *Haemophilus influenzae* Type b Disease at the Beginning of the 21st Century: Global Analysis of the Disease Burden 25 Years after the Use of the Polysaccharide Vaccine and a Decade after the Advent of Conjugates

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BACKGROUND

Vaccination against *Haemophilus influenzae* type b (Hib) began in the 1970s. A capsular polysaccharide vaccine (8, 139) consisting of the polyribosylribitol phosphate (PRP) of the outermost layer of Hib (36), was tested in the field (107, 124, 129). In Finland a 90% efficacy, with 95% confidence intervals ($CI_{95\%}$) of 55 to 98%, was achieved in children aged 18 to 71 months (Table 1) but not in younger children (131).

Similar prospective studies were not conducted elsewhere. The United States and Canada remained the only countries worldwide in which three PRP products were licensed for general use in children aged 24 to 59 months (6, 15, 25a, 73). In addition, parts of Saudi Arabia used PRP temporarily (119). However, PRP proved inferior to newer vaccines in three aspects: it was a poor immunogen in children younger than 18 months (131), it lacked booster effect (107), and it had no clear effect on nasopharyngeal carriage (163). Despite these shortcomings, over 10 million doses of PRP were administered in the United States from 1985 to 1989 (1).

The late 1980s saw the advent of conjugate vaccines against Hib disease. Four modifications of these vaccines became commercially available (7, 29, 62, 108); various combinations with other vaccines were and are continuously released. Diphtheria toxoid conjugate (PRP-D; ProHIBiT) was the first conjugate introduced. It was soon followed by mutant diphtheria toxin conjugate (PRP-CRM or HbOC; HibTITER), meningococcal outer membrane protein conjugate (PRP-OMP; PedvaxHIB), and tetanus toxoid conjugate (PRP-T; ActHIB, OmniHIB, or Hiberix). All conjugates have the same immunologic principle—combination with a carrier protein transforms a T-cell-independent antigen (plain PRP) into a T-cell-dependent one, conferring improved immunogenicity in infancy (9, 148). These conjugates also have an excellent safety record.

The conjugate vaccines are effective tools for preventing Hib infections, which were the most common severe invasive infections of childhood in industrialized countries (34). At least four prospective studies (16, 18, 46, 146) show an efficacy exceeding 90% from the first months of life (Table 1) with only one exception. In contrast to the much larger study in Finland (46), PRP-D did not induce significant protection among Inuits of Alaska (181), whose living conditions are quite dissimilar from the standard in the industrialized world.

A quarter century has elapsed since 1974, when Finland demonstrated the efficacy of the polysaccharide vaccine (131), and it is more than a decade since 1986, when vaccinations with a conjugate were introduced (46). Since then, at least 38 countries have included Hib immunization in their routine childhood vaccination programs (28a). This is well justified because Hib has been shown to be an important cause of life-threatening childhood infections worldwide (126–128).

To date, no one has examined the global change in Hib disease epidemiology and whether Hib diseases are decreasing due to vaccination. This review addresses these critical questions.

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TABLE 1. Protective efficacy of the Hib vaccines in prospective randomized studies

Vaccine	Country	Age (mo) of vaccinees	No. of children vaccinated	No. of Hib cases in:		Efficacy (%)	*P*	$CI_{95\%}$	Reference(s)
				Vaccinees	Controls				
Polysaccharide	Finland	18–71	37,393	2	20	90	<0.001	55, 98	129, 131
Conjugates									
Diphtheria toxoid (PRP-D)	Finland	3, 4, 6	110,000	4	37	94	<0.001	83, 98	46
	U.S.A. (Alaska)	2, 4, 6	2,100	7	12	43	NS	−43, 78	181
Mutant diphtheria toxoid (PRP-CRM, HbOC)	U.S.A.	2, 4, 6	61,080	0	22	100	<0.001	71, 100	16
Outer membrane protein (PRP-OMP)	U.S.A.	≈2, ≈3	4,161	1	14	93	<0.001	53, 98	146
Tetanus toxoid (PRP-T)	U.K.	2, 3, 4	31,983	1	18	95	<0.001	74, 100	18

METHODS

Hib causes a variety of clinical manifestations which affect the central nervous system (meningitis) or localize in only one anatomic site (39, 68, 130). These entities comprise the "classical" Hib diseases, in which the agent can be isolated from blood, cerebrospinal or joint fluid, or other normally sterile body fluid. Because of an inherent problem of diagnosing the etiology of acute lower respiratory infections, nonbacteremic Hib pneumonia will be discussed separately from bacteremic Hib manifestations.

In this study, a comprehensive worldwide analysis of all these complex Hib diseases was performed. There were three major objectives: (i) to identify all major clinical manifestations of Hib disease in different countries and regions of the world (20), (ii) to disclose the global burden of severe Hib diseases in the prevaccination era, and (iii) to delineate the impact of large-scale vaccinations in countries in which they have been carried out.

All clinical and epidemiological data available since the 1960s were collected; older information was not considered. A variety of sources in 10 languages were examined for the data collection: the Medline database, local medical literature (often not in English), and abstracts and posters from international scientific meetings. If data over several years or decades were available from the same area, the most recent data were used.

Most attention was paid to the patient group aged 0 to 4 years, in which approximately 85% of Hib disease occurs (39, 51, 77, 78, 80, 130, 132). Besides the best-known entity, meningitis, all Hib entities such as epiglottitis, nonfocal septicemia, cellulitis, osteomyelitis, and septic arthritis were identified. Hib pneumonia associated with bacteremia was differentiated from pneumonia without bacteremia because several studies from the developing world (3, 115, 122, 152, 180, 183; S. P. Lupisan, H. Nohynek, M. R. Z. Capeding, L. T. Sombrero, G. Esparar, E. Herva, B. P. Quiambao, P. E. Abucejo, L. G. Pascual, J. Arcay, V. L. Tallo, P. H. Mäkelä, and P. Ruutu, Abstr. Int. Conf. Acute Respir. Infect. p. 98, 1997) suggested that the role of nonbacteremic Hib pneumonia may be even greater than that of Hib meningitis (65).

The burden of global Hib diseases in the prevaccination era was quantified in terms of numbers of cases per annum in small children and the entire population including all age groups. These detailed epidemiological data were collected, whenever possible, by a systematic search for information from each region, although it was recognized that reliable data were not always available from Africa, Asia, and the Newly Independent States (187a). Because official reports are often unreliable, the search focused primarily on incidence rates deduced from population-based sources. The total numbers of cases and deaths were estimated from the incidence rates.

The analysis included over 75 areas in more than 50 countries in the six regions categorized by the World Bank: Africa, Asia, Europe, Latin America and the Caribbean, North America, and Oceania (20). According to the same source (20), Asia was defined geographically as the area extending from the Mediterranean Sea in the west to the Pacific Ocean in the east, including Israel, the Middle East countries, and Japan but not Papua New Guinea. Oceania comprised Australia, New Zealand, and the vast archipelago extending from Papua New Guinea in the west to the entire French Polynesia in the east (20). The population statistics of the six World Bank regions are presented in Table 2.

World maps were produced displaying incidence rates as different colors. Since incidence is unlikely to change much in the surrounding population, unless race and general circumstances differed (33, 37, 63, 70, 182), the geographical borders in these maps were depicted by fading the color gradually or changing it to grey when no data were available. Regional and continental figures were calculated as weighted averages. Incidence rates from the same region but with only minor differences were averaged.

Finally, the impact of the Hib vaccines, i.e., the polysaccharide vaccine in the 1970s and 1980s (124, 129, 131) and conjugates subsequently (16, 18, 46, 146), was characterized.

TABLE 2. Total and 0- to 4-year-old populations worldwide[a]

Region	Population		% of population made up of children aged 0–4 yr
	Total	Children aged 0–4 yr	
Worldwide	5,692,210,000	631,082,000	11.1
Developing regions	4,447,966,000	549,160,000	12.3
More developed regions	1,245,234,000	82,911,000	6.7
Africa	719,202,000	121,483,000	16.9
Asia	3,443,274,000	385,639,000	11.2
Europe	730,908,000	43,258,000	5.9
Latin America and the Caribbean	474,843,000	55,163,000	11.6
North America	295,333,000	22,909,000	7.8
Oceania (including Australia)	28,650,000	2,629,000	9.2

[a] Projections for 1995 by The World Bank (20). The numbers are not summed exactly, but the error is negligible (<1%).

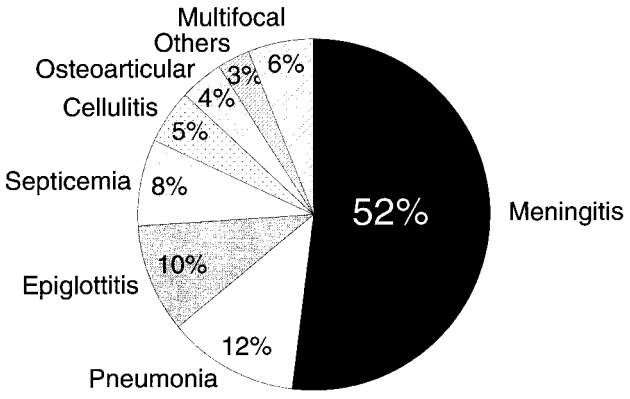

FIG. 1. Worldwide spectrum of all classical (nonbacteremic pneumonia excluded) Hib diseases, taken from data for 3,931 patients in 21 studies from various parts of the world.

RESULTS

Epidemiology Prior to Vaccination

Data obtained for 3,931 patients from 21 studies worldwide in the 1970s to 1990s (Fig. 1) showed that over 90% of invasive (bacteremic) Hib infections manifested as six "classical" entities: meningitis, bacteremic pneumonia, epiglottitis, septicemia, cellulitis, and osteoarticular infections (more often septic arthritis than osteomyelitis). Other clinical manifestations constituted only 3% of the total number, whereas multifocal cases were diagnosed in 6%. Notably, meningitis represented only 52% of the entire Hib disease spectrum.

Meningitis. Meningitis (Fig. 2) was the only Hib disease manifestation for which abundant epidemiological data were available. However, these data were not evenly distributed worldwide, even though 55 countries were represented, including Russia (42, 44), Bangladesh (90, 145, 151), and the People's Republic of China (156, 190, 191), from which information has previously been scanty.

In the United States, the overall annual incidence of Hib meningitis in children aged 0 to 4 years was about 50 to 60 per 100,000 (ranging from 19 to 69 per 100,000) prior to vaccine availability; the average was 54 per 100,000 (23, 31, 33). This incidence was greater than twice the weighted average for prevaccination Europe, 23 per 100,000 (126). The rates in Europe were closer to those characteristic of large parts of South America, Asia, or Oceania: in Rio de Janeiro, Santiago de Chile, two sites in Argentina, Israel, United Arab Emirates, and Malaysia, the annual incidence of Hib meningitis was above 20 but less than 50 per 100,000 in children aged 0 to 4 years (51, 75, 83, 140, 141, 171; A. Torres, A. Bueno, A. Trejoi, and L. Suarez, Abstr. Simp. Int. Infect. Pediatr. 1994, abstr. 174-PP, 1994). The incidence was in the same range in New Zealand and Ontario (Canada) and among the non-Aborigines in Australia (48, 60, 68, 102).

Countries with rates lower than 20 per 100,000 included Uruguay in South America and Hong Kong, Japan, Saudi Arabia, and Qatar in Asia (98, 119, 120, 128, 172). Of note, recent hospital-based estimations from the Philippines (106) and India (84) proposed a rate for Hib meningitis as high as 95 and 50 to 66 cases, respectively, per 100,000 per annum in children aged 0 to 4 years. In fact, a detailed analysis of the data throughout Asia (127) did not lend support to the commonly held view that Hib meningitis would be especially rare there. However, differences between regions in this vast continent were obvious. For example, Hib was responsible for 50% of the documented cases of childhood bacterial meningitis in St. Petersburg in western Russia, but in the more easterly cities it accounted for only 31% in Moscow, 36% in Ekathen-

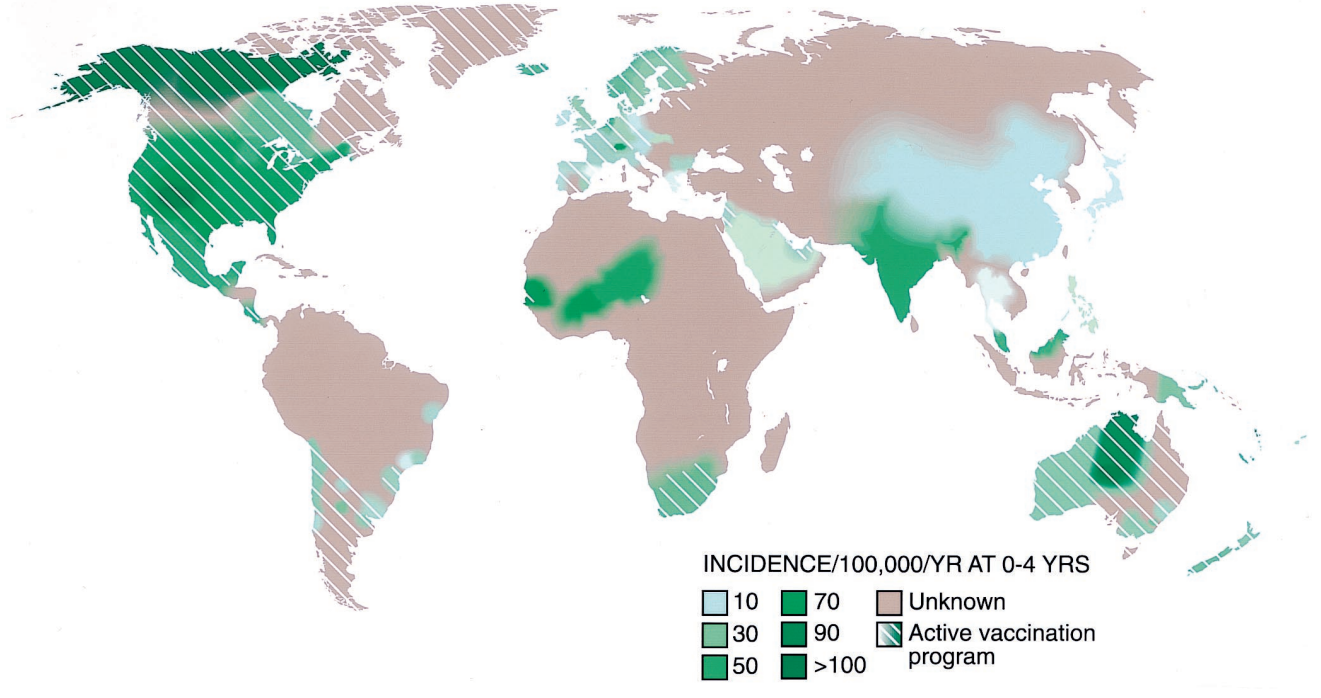

FIG. 2. Worldwide incidence per 100,000 per year of Hib meningitis for children aged 0 to 4 years before the conjugate era. Hatched areas had significant vaccination activity in 1999.

TABLE 3. Estimated worldwide yearly toll of invasive Hib infections before the conjugate vaccine era

Disease	Developed regions[a]		Developing regions[a]		Whole world	
	0–4-yr-old children (83×10^6)[b]	All age groups ($1{,}250 \times 10^6$)	0–4-yr-old children (550×10^6)	All age groups ($4{,}500 \times 10^6$)	0–4-yr-old children (630×10^6)	All age groups ($5{,}700 \times 10^6$)
Meningitis						
Incidence	32	2.5	60	7.5	57	0.7
No. of cases	27,000	32,000	330,000	337,000	357,000	369,000
No. of deaths	1,300	3,200	100,000	101,000	101,300	104,200
Case fatality rate (%)	5	10	30	30	28	28
Epiglottitis						
Incidence	13	1	<1	<1	2	0.2
No. of cases	11,000	13,000	1,000	1,000	12,000	14,000
No. of deaths	200	300	200	200	400	500
Case fatality rate (%)	2	2	20	20	2.5	3
Other entities excluding nonbacteremic pneumonia						
Incidence	12	1	12	2	12	2
No. of cases	10,000	13,000	66,000	90,000	76,000	103,000
No. of deaths	200	500	6,600	9,000	6,800	9,500
Case fatality rate (%)	2	4	10	10	9	9
Pneumonia						
Incidence	6[c]	1	300[d]	45	300	35
No. of cases	5,000	13,000	1.7×10^6	1.7×10^6	1.7×10^6	1.7×10^6
No. of deaths	250	600	220,000–400,000	ca. 400,000	220,000–400,000	ca. 400,000
Case fatality rate (%)	5	5	13–24	13–24	13–24	13–24
Total						
Incidence excluding pneumonia	57	4.5	72	9	71	3
No. of cases excluding pneumonia	48,000	58,000	397,000	428,000	445,000	486,000
No. of deaths excluding pneumonia	1,700	4,000	106,800	110,200	108,500	114,200
Case fatality rate (%)	4	7	25	25	24	23
Incidence including pneumonia	63	5.5	370	55	370	40
No. of cases including pneumonia	53,000	70,000	2.1×10^6	2.1×10^6	2.2×10^6	$>2.2 \times 10^6$
No. of deaths including pneumonia	2,000	4,650	325,000–500,000	510,000	340,000–515,000	>520,000
Case fatality rate (%)	4	7	15–25	20	15–23	20

[a] World Bank categorization (20).
[b] Values in parentheses give the populations for each group.
[c] Probably an underestimate.
[d] Applying the earlier conservative Gambian estimate (65), which is lower than that reported later in Gambia (115) or in Papua New Guinea (101), and closer to that among Australian Aborigines (68).

burg, and 30% in Siberian Arkhangelsk in the same survey (42, 44).

Among native populations in Alaska, northern Canada, and central and northern Australia, the yearly incidence in children aged 0 to 4 years exceeded 150 per 100,000 and was sometimes considerably higher (67, 68, 70, 182). The risk for Hib meningitis was also somewhat greater among Bedouins in Israel, as well as the Maoris and Melanesians in Oceania and Mapuche children in Chile (17, 141, 177).

The difference in cumulative incidence between indigenous and white populations was especially striking in Australia. The median age for contracting Hib meningitis in Aborigines was 6 months, with nearly 60% of cases occurring in the first 7 months of life; the equivalent numbers in non-Aborigines were 15 months and 17%, respectively (69). In Senegal, Africa, the incidence rate among 0- to 11-month-old infants was twice that in the entire cohort of children aged 0 to 4 years for this country (25). In Gambia, this difference was fivefold: 297 per 100,000 and 60 per 100,000, respectively (13).

The highest reported incidence of meningitis was in the Keewatin District of Canada: 530 per 100,000, mostly in the Inuit population (67). Rates exceeding 200 per 100,000 were also observed in Alaska, in Australian Aborigines, and in Native American and black populations in the United States, but such high rates were not found in Africa, where the rates, e.g., 72 per 100,000 in children aged 0 to 4 years in Senegal (25), were comparable to the prevaccination U.S. average.

If incidences of 32 and 60 per 100,000 in children aged 0 to 4 years are applied to the world's "more developed" and "developing" regions, respectively (20), the annual number of cases of Hib meningitis would be 27,000 and 330,000, respectively, for a total of 357,000 cases worldwide (Table 3); these numbers are 51% higher than the previous estimation of 236,000 annual cases of Hib meningitis in this age group (118).

No major changes in meningitis mortality have occurred during the past decades, despite some arguable benefit of the early use of dexamethasone as adjunctive therapy (91, 99, 179). A 5% case fatality rate suggests some 1,300 deaths annually in children from birth to 4 years of age in developed regions before the vaccination era (Table 3).

At the same time, the situation was dramatically worse in the developing world—even in the 1980s, 63, 37, 38, and 30% of patients with Hib meningitis died in Ghana, Gambia, northeastern Brazil (Bahia), and Papua New Guinea, respectively (13, 24, 64, 188). In Gambia, the mortality attributable to Hib meningitis was calculated as 23 per 100,000 per year, a rate as high as the incidence of Hib meningitis in Germany before vaccinations were begun (65, 82). If a 30% mortality is assumed, 100,000 deaths from Hib meningitis occur each year in developing regions (where Hib vaccines are used very little [Table 3]); this number is 163% greater than the previous estimate (118).

Worldwide data on sequelae were not available. A meta-analysis that reflected the situation in some high-quality treatment centers showed permanent sensorineural hearing impairment in 11.4% of patients following Hib meningitis (54). Even with the best care, 27% of children surviving bacterial meningitis had disabilities that affected their academic performance (66, 69). Again, the situation in developing countries was gloomiest: in Gambia, only 55% of children with Hib meningitis recovered completely, and in Colombia, 56% of survivors developed neurological sequelae (13; E. Parra and U. Castro, 1st World Congr. Pediatr. Infect. Dis., poster C-054, 1996). More startlingly, 24% of Bangladeshi children who seemed to have survived bacterial meningitis, almost certainly many caused by Hib (145, 151), had died when checked 3.5 months later (90). An estimated overall incidence of 30% for sequelae caused by Hib meningitis suggests that at least 100,000 patients a year are affected, with the majority being left hearing impaired.

Epiglottitis. Epidemiologic data on acute epiglottitis, the second most common Hib disease in industrialized countries, have been available from 19 countries since the 1970s. In Switzerland, the annual incidence was the highest reported, 30 per 100,000 in children aged 0 to 4 years (113). In Göteborg, Sweden, epiglottitis was reported to be as common as meningitis, with the rates in this age group being 28 and 27 per 100,000, respectively (30). Also, the annual incidence of epiglottitis exceeded 20 per 100,000 in some states of Australia (60).

During the prevaccination era, epiglottitis tended to occur later in life than meningitis. Assuming incidence rates of 13 and 5 per 100,000 in children aged 0 to 4 and 0 to 14 years, respectively, the rates were 13.2 and 5.3 per 100,000, respectively, in Finland (165). The estimated numbers of cases in the more developed regions were 11,000 in children under 5 years and 12,500 in those under 15 years.

In developing regions, there was an inverse trend between meningitis and epiglottitis. Epiglottitis was virtually absent among Australian Aborigine, Alaskan and Canadian Inuit, and African children (48, 68, 78, 182) and was exceedingly rare in children in other developing regions (51, 75). If 1,000 cases occurred annually in children aged 0 to 4 years in the developing world, the global number was 12,000 cases of epiglottitis per year (Table 3). Since most cases occurred in countries with good resources for emergency transportation and intensive care, epiglottitis was rarely fatal and usually did not cause sequelae. In a large Swedish series comprising 808 cases, the overall case fatality rate was 2% and no sequelae were observed (11).

Other classical Hib manifestations. Except for epiglottitis (which was rare in developing countries and indigenous populations), the distribution of the classical Hib manifestations was roughly the same wherever it was studied. Incidence data for each specific disease were scanty. In Finland, septic arthritis among 0- to 4-year-old children occurred in 5 per 100,000, cellulitis occurred in 4 per 100,000, bacteremia without an identifiable focus occurred in 2.4 per 100,000, and pyelonephritis occurred in 0.6 per 100,000 per annum (164). In Israel, the rates of cellulitis and bacteremia were 4 and 3 per 100,000 per annum, respectively (37). In New Zealand, the annual incidence of orthopedic infections, cellulitis, and bacteremia was 3, 2, and 1 per 100,000, respectively (177). Among non-Aborigines in Australia, the rates of bacteremia and septic arthritis were 9 and 7 per 100,000, respectively, but among Aborigines they were manyfold higher: 99 and 33 per 100,000, respectively, and 13 per 100,000 for other manifestations (68).

Hence, a yearly incidence of 12 cases per 100,000 in children aged 0 to 4 years in both developed and developing regions seems a reasonable estimation. If so, there were 10,000 and 66,000 cases per year, respectively, making up 76,000 cases in this age group (Table 3). Combining all age groups, there were probably more than 10,000 cases per annum of these lesser-known Hib diseases.

Figure 3 summarizes information on classical Hib diseases from 75 regions in 36 countries. Indigenous populations suffered the highest toll: the Aborigines of central Australia showed an annual incidence of 1,100 per 100,000 in children aged 0 to 4 years (70); the rate was later confirmed as 991/100,000 per year (69). Around 15 to 20% of these cases were not caused by type b strains, in contrast to Alaskan Inuits, in whom virtually all strains were Hib (182). In this exceptionally vulnerable population, the annual incidence of Hib diseases exceeded 0.5% in the entire child population, being 601 per 100,000 (182).

In industrialized countries, a relatively high incidence of the classical manifestations was observed. For example, in the United States the combined average was 88 per annum in children aged 0 to 4 years, although again with wide interpopulation variation (31). In Europe, 107 cases per 100,000 per annum were found in Switzerland, followed by 80 cases per 100,000 in The Netherlands (59, 74). For Europe in general, the yearly incidence of the classical Hib diseases in children aged 0 to 4 years was 41 per 100,000, versus an estimated 60 cases per 100,000 for Latin America and the Caribbean and 40 per 100,000 for Asia (126–128).

Pneumonia. The incidence of Hib pneumonia among some populations aged 0 to 4 years was deemed low, only 1 and 3 per 100,000 in Finland and northern New Zealand, respectively, and 7 per 100,000 in both Israel and non-Aborigines in Australia (37, 68, 164, 177). However, these rates primarily reflected only bacteremic cases. Proving the etiology of the more common nonbacteremic pneumonia is cumbersome, costly, and often impossible (50, 52, 143). It is very likely that pneumonia, particularly nonbacteremic pneumonia, is the major Hib disease worldwide because its incidence, especially in small children, is greater than that of meningitis.

A phenomenally high incidence of culture-proven Hib pneumonia, 2,860 cases per 100,000 (almost 3%) per year in children aged 0 to 4 years, was reported from Papua New Guinea (101). This rate was considerably higher than among Australian Aborigines (225 per 100,000) and four- to fivefold higher than the incidence of all classical Hib diseases among Alaskan Inuits (68, 182). Since the Papua New Guinean estimate was based on a small case series, one may argue its applicability to other regions. Nevertheless, earlier data from Gambia showed

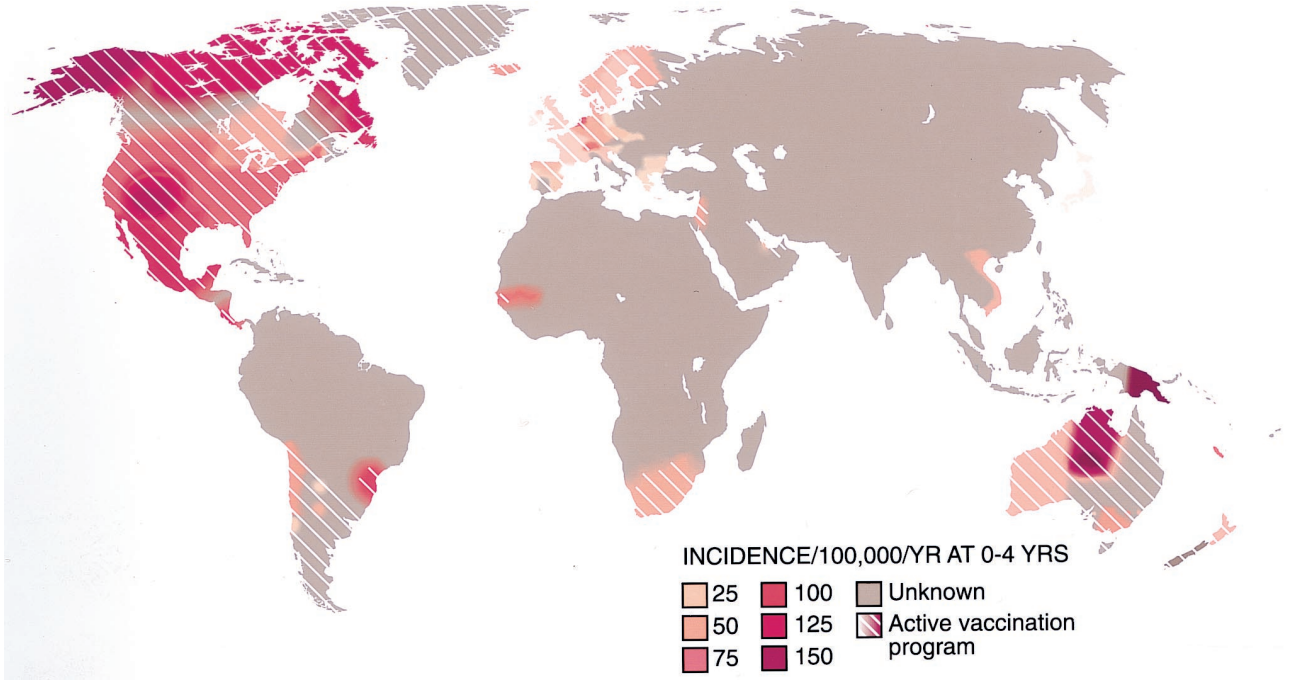

FIG. 3. Worldwide incidence per 100,000 per year of all classical Hib diseases for children aged 0 to 4 years before the conjugate era. Hatched areas had significant vaccination activity in 1999. Note that nonbacteremic pneumonia, probably the most common Hib manifestation worldwide, is mostly neglected because very few reliable data are available.

that *H. influenzae* was the second most common cause of pneumonia, with 75% of the strains being type b (65, 180). In Pakistan (183) and Papua New Guinea (64, 152), many *H. influenzae* isolates were not Hib whereas in the Philippines, Hib was 30% less common than pneumococci in blood culture-positive pneumonia (170).

The studies in which lung tap (aspiration) has been used to detect the etiology of childhood pneumonia are of special interest. For decades, this technique has been used mostly but not exclusively in developing countries (E. Vuori-Holopainen and H. Peltola, submitted for publication). Unfortunately, specific information on Hib is meager, because serotyping has usually not been done. Otherwise, the role of *H. influenzae* is indisputable. For example, *H. influenzae* was the second leading cause of culture-proven bacterial pneumonia in children in Latin America (52, 110, 122, 142, 149).

Data on Hib among other causative agents of pediatric pneumonia traced by lung tap were available from Colombia (122), Gambia (3, 115, 180), Papua New Guinea (64, 152), and the Philippines (Lupisan et al., Abstr. Int. Conf. Acute Respir. Infect., 1999). Hib was responsible for 12 to 75% of cases due to *H. influenzae*. In Gambia, when all lung tap- or blood culture-proven cases were included, 54 to 79% of cases of *H. influenzae* pneumonia were attributable specifically to Hib (3, 180). Thus, worldwide figures on Hib infections that do not include nonbacteremic pneumonia would be gross underestimates of the total Hib burden.

On the other hand, an elegant study from Papua New Guinea (64) demonstrated that the lung, due to its proximity to the densely colonized upper respiratory tract, is more easily invaded by less invasive organisms such as non-type b *H. influenzae*. For this reason, supposedly, 80% of the lung tap isolates in that country were types other than Hib. This study found that 38% of blood isolates and 18% of cerebrospinal fluid isolates were non-type b. Even these two latter figures are high compared to those found in other countries, in which Hib is usually responsible for around 95% of cases of *H. influenzae* septicemia or meningitis.

A recent vaccine study in Gambia (115) has added much to our understanding on the role of Hib in pediatric pneumonia. A Hib conjugate vaccine decreased severe childhood pneumonia by approximately 25% (115); hence, about one-quarter of all cases of life-threatening pneumonia of childhood, not only of *H. influenzae* pneumonia, might be caused by Hib, at least in developing countries. This view is in good agreement with the lung tap studies.

Generalizing for all developing regions, the Gambian estimate of the incidence of pneumonia (acute lower respiratory infection) from the early 1990s, i.e., 300 episodes per year per 100,000 in children younger than 5 years (65), would result in 1,650,000 cases per annum. The rate is fivefold that of Hib meningitis worldwide (Table 3). This estimate may be considered conservative if up to 25% of cases of severe pneumonia of childhood are caused by Hib (115). Studies from six developing countries indicated 0.2 to 4.0 episodes of pneumonia per year during the first 5 years of life (143, 150). If an incidence of only two episodes per year is assumed, this would result in 1.1 billion cases per annum. If only a small portion of these were caused by Hib (115), the worldwide number of cases of Hib meningitis would still be in the millions per year.

The death toll from Hib pneumonia was equally difficult to estimate. *H. influenzae* and pneumococcal pneumonia combined accounted for more than 40% of deaths in children in Papua New Guinea (152). In Gambia, there were 40 per 100,000 deaths from Hib pneumonia in children aged 0 to 4 years (65). Since 10% (65) or perhaps significantly more (115) of the over 4 million annual pneumonia deaths in this age group (103) are due to Hib, the number of deaths is 220,000 to 400,000 in developing countries; the worldwide total would include a few more in the industrialized world (Table 3). The

incidence of death from Hib pneumonia in Gambia, 40 per 100,000, was as high as the incidence of all classical Hib diseases in Denmark or New Zealand (94, 177).

Total incidence and mortality. Hib diseases do not affect the 0- to 4-year-age group exclusively (186). In older adults and immunocompromised individuals, invasive Hib infection is often fatal; in one series, the overall mortality was 26% (162).

In prevaccination Finland, 16 and 9.5% of the classical Hib manifestations occurred in persons older than 4 and 14 years of age, respectively, whereas for Hib meningitis the figures were 10% and 3%, respectively (131). In South Korea, 8 to 14% of cases of Hib meningitis occurred in persons older than 5 years (100). In the United States, 12% of Hib disease was in adults, and the annual incidence for the whole population was 4 per 100,000 (49, 187); for Hib meningitis, the rates varied between 7.7 and 2.8 per 100,000 (185). Similar to Finland (132), the total incidence in Sweden was around 5 per 100,000 per year (77). Assuming an incidence of only 5% for Hib meningitis in persons older than 4 years, 369,000 cases a year may have occurred worldwide in all age groups prior to the vaccination era.

Worldwide estimates for epiglottitis and for the other Hib diseases except meningitis, epiglottitis, or pneumonia were 14,000 and 103,000 per annum, respectively. For reasons stated above, the number of cases of Hib pneumonia was difficult to estimate. Applying the earlier conservative Gambian estimate of about 300 episodes of pneumonia per year in children aged 0 to 4 years (65) (which is lower than the later estimate in Gambia [115] or the incidence in Papua New Guinea [101] but close to that among Australian Aborigines [68]), 1.7 million cases per year are estimated (Table 3). The vast majority of these cases were in developing countries.

Table 3 summarizes the global estimates of the Hib disease burden in the prevaccination era. The incidence of all classical Hib diseases was likely to be around 71 per 100,000 in children aged 0 to 4 years and 3 per 100,000 for all age groups; these rates result in 445,000 and 486,000 cases per annum, respectively. Over 114,000 patients (23%) died, 90% from meningitis; about an equal number of sequelae could be assumed.

If nonbacteremic Hib pneumonia is included in calculations, the worldwide incidence for all Hib manifestations changes drastically. It is most likely that not less than 370 cases per 100,000 occurred per annum in children aged 0 to 4 years and 40 cases per 100,000 occurred in all age groups. Conservatively estimated, Hib diseases totalled over 2.2 million cases a year, perhaps 10- to 100-fold more (see above). The death toll might have been well over 520,000, or 23%.

Impact of Vaccination

The past era of polysaccharide vaccine. Since the only controlled field trial of PRP in a sufficiently large study population in the 1970s (131) showed no efficacy in children younger than 18 months (Table 1), Finland never licensed PRP for general use. Hence, no impact could be measured. However, based on the epidemiological characteristics for Finland that less than 10 and 30% of infants with Hib meningitis develop disease during the first 6 and 12 months of life, respectively, 60% of Hib disease could have been prevented by the routine use of PRP. The same calculation might have applied to countries such as Austria, where Hib meningitis essentially starts at the age of 6 months and only 20% of cases develop before the first birthday (137).

Although the rather wide use of PRP in the United States and Canada provided an opportunity to measure the impact in North America, data from the United States were surprisingly difficult to interpret. In Texas, Pittsburgh, and Connecticut, the protection rate was 89% (154), but in Minnesota the rate was −55%, albeit with extremely wide $CI_{95\%}$ values from −238 to 29% (123). Data from several case control studies showed point estimates oscillating between 45 and 88% (15, 72, 73).

There is no adequate explanation for such an immense variation in the effectiveness of the polysaccharide vaccine. It is, however, likely that if the vaccine was only moderately effective, a series of studies could yield a wide range of point estimates. On the other hand, regional differences in immunologic priming by gastrointestinal colonization with cross-reacting enteric bacteria might also have played some role (184). The same phenomenon may partly explain the excellent immunogenicity of various Hib vaccines in some countries in Latin America and Southeast Asia (96, 100), countries well known to have endemic enterobacterial diseases and epidemics. Genetic differences in the population were less likely to explain the differences, since Minnesota has a large population with a Scandinavian background and there was no difference in immunogenicity between the vaccine lots used in Finland and the United States (88).

Before the licensure of PRP in 1986, there were 19,500 cases of Hib disease in children aged 0 to 4 years in the United States (32). Although some spontaneous decrease in the incidence had occurred after 1984 (1), the number of cases in 1988 was 12,000 (184), a 38% decline. There is no reason to suspect that PRP played no role in this progress. In Canada, the number of Hib cases found in several tertiary-care hospitals also decreased by 38% from 485 in 1985 to 300 in 1988, the year when the first conjugate PRP-D was licensed (80).

(i) PRP measurements as surrogate markers for protection. Whatever the ultimate impact on Hib diseases, the use of PRP vaccine provided fundamental new information. For example, it was shown (87) that the use of PRP does not induce immunologic tolerance, which was deemed a potential problem in infants who do not respond sufficiently to polysaccharide antigens.

From studies in the 1970s and 1980s (87–89, 107, 129, 131), it was also learned that short-term and long-term protection against Hib infections is achieved by anti-PRP concentrations of 0.15 and 1.0 μg/ml, respectively (89). In a nonvaccinated population, the limit of 0.15 μg/ml showed a good inverse relationship with the incidence of disease, suggesting a sufficient amount of antipolysaccharide antibodies. Because an anti-PRP level of 1.0 μg/ml more appropriately reflected protection in the vaccinated population (89), this finding suggested that vaccination does not elicit qualitatively such effective antibodies as those induced by natural Hib disease.

These antibody limits are not directly applicable to conjugate vaccines, which trigger T-cell-dependent immunity, in contrast to polysaccharide vaccine, which is a typical T-cell-independent antigen (9, 87, 148). The strong immunogenicity of conjugates is observed by a good booster response of a vaccinee to a challenge by plain PRP, a situation that mimics natural Hib infection.

The effectiveness of this response was demonstrated in Finland in the late 1980s (46, 134), when the poorly immunogenic conjugate PRP-D (40), the only conjugate then available, was used in 1986 to 1987. Only 50% of infants were vaccinated, but still a 94% ($CI_{95\%}$, 83 to 98%) clinical efficacy was achieved (Table 1). The protection was much better than predicted by serology, since an antibody level of 1.0 μg/ml was reached only in 29% of vaccinees; even the low concentration of 0.15 μg/ml was reached only in 58% of the PRP-D recipients.

Hence, to what extent are the PRP measurements applicable to conjugates? In principle, a person immunized only once with

a Hib conjugate should respond with a rapid antibody response, even though the antibody levels in serum would have waned; in fact, better than 50% protection is achieved after one vaccine dose (134). Evidently, the antibody measurements that were once so useful in the context of PRP give too pessimistic a view of the clinical protection elicited by conjugates. However, no better surrogate markers for clinical effectiveness have thus far been produced than the measurement of anticapsular antibodies. Importantly, measuring the booster effect after post-primary vaccine doses seems to predict clinical protection moderately well.

The present era of conjugate vaccines. Few vaccines in history have induced such a dramatic decline in incidence over such a short period as have the Hib conjugates. The ability of these vaccines to prevent nasopharyngeal Hib colonization under most (86, 112, 113, 116, 163, 166), though not all (5; K. Galil, R. Singleton, O. Levine, M. Fitzgerald, G. Ajello, L. Bulkow, and A. Parkinson, Abstr. 35th Annu. Meet. Infect. Dis. Soc. Am. 1997, abstr. 421, 1997), circumstances partly explains these good results (Table 1; also see Table 4).

Hatched areas on the maps (Fig. 2 and 3) show that Hib vaccination is included in routine infant immunization programs in the United States, Canada, Mexico, Costa Rica, Chile, Argentina, Curitiba (Brazil), Uruguay, several European countries, Gambia, South Africa, Israel, several Gulf states, Australia, New Zealand, and some other smaller countries or regions. In light of these programs, what has been achieved in a decade? The data obtained from 22 countries representing all continents are summarized in Table 4 and discussed below.

(i) Europe. After the first trials with PRP-D conjugate in 1986 and 1987 (45, 46, 134), Finland accomplished the only controlled follow-up study 2 years later, in which two conjugates, PRP-D and PRP-CRM, were compared side by side (134). Both conjugates proved effective, since no cases of Hib disease occurred in either group after three doses. The impact of vaccination was indisputable: within a few years, the incidence of all diseases in which Hib plays a major role, i.e., meningitis, epiglottitis and septic arthritis, declined to a fraction of the previous levels (133, 135, 165). This success has also had direct implications for the treatment of patients: eliminating Hib as a cause allows the selection of a narrower-spectrum antimicrobic (for example, cephalexin or clindamycin) to treat acute osteoarticular infections (135).

Iceland launched a program of vaccination with PRP-D in 1989, and Hib diseases disappeared within 3 years (85, 86). Denmark, Norway, and Sweden instituted their programs later (57). In Scandinavia (Table 4), at least 470 cases of meningitis and 770 cases of all classical Hib diseases are prevented annually (136).

In Germany, several postmarketing studies indicate a similar trend. In the Rhein-Main area, the incidence of all Hib diseases in children aged 0 to 4 years decreased from 33 to 6 per 100,000 within 24 months, a 94% decline (82, 189); a further decline has occurred since then (176a). The same trend occurred in The Netherlands, where the current incidence of Hib meningitis is only 0.3 per 100,000. In Switzerland, which once had the highest rate in Europe, the rate has remained somewhat higher, 5.7 per 100,000 in 1993 (43, 113).

The same has happened in the United Kingdom, which launched general PRP-T vaccination in 1992 (18, 19). Effectiveness was first observed in the northeastern Thames region (173) and soon spread throughout all of England and Wales (71, 167), where the incidence of all classical Hib diseases in children aged 0 to 4 years is now 2 per 100,000, or less. The decline has been greater than 97% (19).

France has used exclusively PRP-T (10). In the Val-de-Marne region, the incidence of classical Hib diseases decreased from 21–25 per 100,000 in children aged 0 to 4 years to 4 per 100,000, indicating a decline approaching 90% (138; J. Boucher, C. Ethenevaux, B. Fritzell, and P. Reinert, Abstr. 21st Int. Congr. Pediatr., 1995). In all of France, the yearly incidence of Hib meningitis in this age group is currently around 2 per 100,000 (10). Once Ireland and Austria had started to use these vaccines, steeply declining incidence rates were observed as well (53, 93). Spain followed the same path, and effectiveness was soon seen in the Basque region, where the incidence of Hib meningitis and all classical manifestations in children aged 0 to 4 years decreased from 14 and 21 per 100,000, respectively, in 1993 to 1995 to 0 and 2 per 100,000 in 1997, respectively (J. Arístegui and N. Muniozguren, Abstr. 20th Congr. Esp. Extraord. Pediatr., 1998).

What remains for the future is the implementation of Hib vaccines in the regular immunization program in populous countries such as Turkey, Poland, and Ukraine (Fig. 2 and 3). In fact, all Newly Independent States lack an efficacious Hib immunization program, although vaccines are available. Although 6,000 cases of Hib disease are prevented in Europe yearly (Table 4), this still represents only one-third of the cases occurring in children aged 0 to 4 years (127).

(ii) The Americas. Once PRP-CRM (HbOC) and PRP-OMP had been licensed for 2-month-old infants in the United States in 1991 (81), the decline in the incidence of Hib diseases that had started as a result of vaccination at age 15 to 60 months quintupled. Since then, the sequence has been spectacular: Hib cases registered by the Kaiser Health Plan in Southern California decreased from 53 to 2 cases in 3 years (175); the incidence of all classical Hib manifestations declined by 92 and 85% in Dallas and Minnesota, respectively (117); and among U.S. Army children, the annual incidence of Hib meningitis declined from 59 to 6 per 100,000 (22). The overall incidence of this entity in the United States has been lowered by 98% among children 4 years of age or younger (14), and currently stands at 1.6 per 100,000 per annum. In the prevaccine era, the average incidence was 88 per 100,000 per year, and 19,500 cases of Hib disease were reported annually in young children (31, 32). The savings through the use of conjugates amounted to $500 million in 1992 (157). Complete elimination of Hib disease, however, has not been achieved; around 300 cases continue to be reported annually (14, 27).

No similar data were available from Canada, but there is no question that the success has been comparable. PRP-D was licensed in 1988, when there were 300 Hib yearly cases in the hospitals participating in the Immunization Monitoring Program (80, 119a). Despite the use of the poorly immunogenic vaccine in those years, the number of cases still declined at an annual average of 21%. Between 1992 and 1993, a decrease of 64% in the incidence of Hib diseases occurred, following the introduction of the PRP-T and PRP-CRM conjugate vaccines for infants aged 2 months across Canada (80, 119a). In 1996, only 10 cases of Hib diseases were encountered, 98% fewer than in 1985 (D. W. Scheifele, personal communication)—exactly as in the United States. Approximately 1,700 cases of severe Hib infections are now avoided annually in Canada (Table 4).

Chile was the first country in Latin America to show the benefits of Hib vaccination. PRP-T also prevented pneumonia, a phenomenon that was not necessarily expected in a nonbacteremic process such as most cases of pneumonia. A 90% decline in Hib disease was observed (96). In Costa Rica, the use of conjugates, first in the private sector and then on a routine basis for all infants, resulted in a 57% decline in ad-

TABLE 4. Annual cases prevented by conjugate vaccines in children aged 0 to 4 years[a]

Area and yr of comparison	No. of children 0–4 yr old	Incidence before vaccination[b]		No. of cases/yr before vaccination		Incidence after vaccination[b]	
		Meningitis	All entities	Meningitis	All entities	Meningitis	All entities
Europe							
Scandinavia,[c] 1970s vs. 1995	1,581,000	31	51	490	810	<1	≈1
Austria, Vienna, 1991 vs. 1993–1996	485,000	11		55		<1	
France							
Val-de-Marne, 1980s vs. 1992–1993	45,000		21–25		18		≈4
Whole country[d]	3,777,000		23	>500	870		≈4
Germany							
Rhein-Main area, 1989 vs. 1993–1995	100,000		33		33	0.8	1
Whole country[d]	4,115,000	23	46	950	1,900	0.9	1.3
Ireland, 1991–1993 vs. 1995	260,000		25		65		2.6
The Netherlands, 1970s vs. 1993–1994	981,000	22–40	80	390	780	0.3	≈1
Spain, Basque region, 1993–1995 vs. 1997	80,000	14	21	13	18	≈0	2
Switzerland, 1976–1990 vs. 1991–1993	447,000	26	84	115	375	8	≈10
United Kingdom							
England and Wales, 1991–1992 vs. 1993–1994	3,434,000	15	31	515	1,060	0.6	2
Whole country[d]	3,831,000	24	36	920	1,380	0.6	≈1
The Americas							
North							
Canada, 1985 vs. 1994[d]	2,026,000	≈44	≈85	≈900	≈1,750	<1	≈2
United States							
20 states, 1980s vs. 1991	7,600,000	19–24		1,334–1,762		3.7	
Minnesota, 1983–1987 vs. 1991			62		210		11
Dallas County, 1983–1987 vs. 1991		91		150		9	
Whole country, 1987 vs. 1995	20,524,000	54	88	12,000	19,500	<1	1.6
South							
Brazil, Curitiba, 1988–1996 vs. 1997	125,000	22		29		10	
Chile, 1995 vs. 1998	1,500,000	40		580		<2	
Costa Rica, 1992 vs. 1994	417,000	≈45	≈100	63	79		
Uruguay, 1992–1993 vs. 1995	261,000	17–22		43		1	
Asia							
Israel 1989–1992 vs. 1995	566,000	18	34	90	170	<1	<1
Qatar 1991–1996	50,000	≈20		10		<2	
Oceania							
Australia							
Sydney region, 1991–1992 vs. 1993–1994	264,000	21	42	55	110	6	16
Whole country[d]	1,360,000	25	59	340	800	6	16
Total	42,386,000				≈24,000		
Estimated elsewhere in Europe and in other countries with significant vaccination activity							
Grand total							

[a] Mostly my own estimations.
[b] Incidence per 100,000 per year.
[c] Denmark, Finland, Iceland, Norway, and Sweden; information analyzed in detail in reference 136.
[d] Assuming a similar effect to that in the given areas.
[e] C. M. Odio, E. Mohs, L. Ramírez, M. Herrera, and I. Faingezicht, Pediatr. Res. **31:**98A, 1992 (abstract).

TABLE 4—*Continued*

No. of cases prevented by vaccination/yr		Reference(s)
Meningitis	All entities	
470	770	136
50		93, 178
	15	138; Boucher et al., abstract
420	720	
900	1,800	82, 176a, 189
	60	53
385	770	5, 74
13	16	Arístegui and Muniozguren, abstract
80	330	43
500	990	18, 19, 71, 167, 173
895	1,340	
880	1,710	80; Scheifele, personal communication
≈1,200		175
	175	117
130	135	117
11,800	19,200	14, 28, 31
19		17a
560		9a
40	45	26; Odio et al., abstract[e]
35		126
≤90	165	37, 38
8		Levine, personal communication
40	70	Hogg et al., abstract
300	580	31, 109; Hogg et al., abstract
≈16,000	≈28,000	
5,000	10,000	
≈21,000	≈38,000	

missions of patients with Hib disease to the only tertiary-care hospital in the country (26). Uruguay was the first country in Latin America to execute a successful countrywide program; the incidence of Hib meningitis in children aged 0 to 4 years declined from 17–22 per 100,000 in 1992 and 1993 to 1 per 100,000 in 1995 and 1996 (126). Chile, Argentina, Mexico, and Colombia have more recently introduced Hib vaccination in their childhood immunization programs, and Chile (9a) has already countrywide figures (Table 4). The Curitiba region of Brazil is an example of successful local vaccination in a large country whose resources did not permit routine immunization for all infants at once (17a).

(iii) Asia, Oceania, and Africa. Israel began large-scale Hib vaccinations in 1992, and a 95% decrease in the incidence of Hib disease was observed (38). In Qatar the decline has been 80% to date (O. S. Levine, personal communication). While most of the other Gulf States have also started Hib immunization (M. Al Musaun, Abstr. Gulf Cooperation Counc. Meet., 1998), many large countries on the Asian continent are not seriously considering wide-scale vaccinations; these nations believe that Hib diseases are not a major issue there (128). In contrast, in Saudi Arabia, it is thought that only compulsory vaccination will guarantee long-term effectiveness against Hib disease (119).

Australia commenced Hib vaccinations in 1992. PRP-CRM was first selected, except for the Aboriginal population, for which PRP-OMP was used. When half of the targeted vaccine coverage was achieved in the Sydney region in 2 years, the incidence had declined by two-thirds (109). In Victoria, the incidence of Hib disease in infants aged 6 to 18 months decreased by 75% between 1991 and 1994 [G. G. Hogg, J. Thompson, J. Carnie, and R. Lester, Aust. Microbiol. **15(4):** A95, 1994]. Close to 600 cases per year are prevented in Australia at present (Table 4). New Zealand is in the same situation, as are some smaller regions in Oceania.

Until recently, Gambia was the only country in Africa that had introduced Hib vaccination into the national immunization program. This was made possible by external financial aid, stimulated by the prospective efficacy study using the PRP-T conjugate (115). As a consequence, the incidence of Hib disease has been declining. In 1999, South Africa became the second country in Africa to combat Hib diseases by systematic vaccination, also with PRP-T. Thus, Gambia and South Africa are forerunners among the over 50 countries in Africa, where more than 95% of the pediatric population receives no Hib vaccine.

(iv) Global impact. Hib conjugate vaccines have essentially been used only by affluent countries and people in the private sector who can afford these vaccines. A combination of the data from 21 countries listed in Table 4 (where Scandinavia is taken as a whole [see reference 136 for details]) and inclusion of estimated vaccinations administered sporadically in other regions results in an estimate that 21,000 cases of meningitis and 38,000 cases of all classical Hib diseases in children aged 0 to 4 years are prevented annually in the affluent world (Table 3). This is 78% of the cases of meningitis in this age group (21,000 of 27,000), or around 50% of the cases of Hib disease in all age groups (38,000 of 70,000) in developed regions.

The worldwide figures are less impressive. Only 5.9% of cases of meningitis (21,000 of 357,000) or 8.5% of cases of the classical Hib manifestations (38,000 of 445,000) in children aged 0 to 4 years are estimated to be prevented by the present vaccination practices. For all age groups, the numbers are 5.7% (21,000 of 369,000) and 7.8% (38,000 of 486,000), respectively.

If pneumonia is included, and for developing countries in general, the numbers fall considerably. The global impact of

Hib vaccination, after more than 10 years during which conjugates have been available, has been negligible. Annually, less than 2% of cases of Hib disease (38,000 of >2.2 million) are prevented worldwide. Since the global population reached 6 billion in 1999, the percentage is even lower. At the advent of the third millennium, some 175 countries and 118 million children (28a) are left without protection against life-threatening Hib infections.

CONCLUSIONS

Hib disease, with its many characteristics, is a complex issue (153). Problems exist in the clinical (Fig. 1) and bacteriological (144) diagnosis of the different manifestations of Hib disease. Reporting is often far from reliable, sequelae remain undiagnosed, and even mortality might be greater than estimated here, since many patients especially in rural areas of poor countries die at home without seeking medical attention (65, 115). However, gathering information over several decades from various sources and reviewing the literature in 10 languages gave a picture which probably is quite realistic. Furthermore, the language bias (111) was avoided by including a number of data published in tongues other than English. Beyond any doubt, Hib diseases continue to be rampant; they have not been eliminated otherwise than locally (Table 4).

The greater case and mortality numbers presented here (Table 3) challenge previous calculations (12, 118) but agree with the recent gross estimation by the World Health Organization that Hib causes at least 3 million cases of serious disease and 400,000 to 700,000 deaths in young children per year worldwide (187a). The data in this review show, for the first time, in detail how these numbers are reached worldwide. The number of cases of Hib meningitis approaches 400,000 per year, and with the other classical manifestations the number increases almost to half a million. The vast majority of cases affect children younger than 5 years. Over 114,000 patients die, and at least as many are left with persistent sequelae.

When nonbacteremic pneumonia is included, the numbers are far greater (Table 3). The calculations may still be underestimates, since appropriate cultures were not used in all cases (144) or the cultures may have remained negative due to prior antimicrobic therapy, which is common practice in many parts of the world. The illusion generated by the spectacular success of conjugates in some countries (Table 4) is grim: while the goal of eliminating invasive Hib disease among children younger than 5 years by 1996 was declared in the United States (28), which goal was not quite reached (14), millions or perhaps tens of millions of children elsewhere suffer from and succumb to the same diseases. Invasive Hib diseases belong to the same global health category as measles, which also causes millions of cases and around 1 million deaths per year (58).

The grey areas on the Hib maps (Fig. 2 and 3), which indicate that no incidence data were available, are disturbing because most children live and most Hib disease occurs in these regions. Information from industrialized regions should be applied with the utmost caution to drastically different circumstances. Fortunately, studies with valuable results have been carried out in Latin America (summarized in reference 126), rural Africa (2, 13, 65, 115), and Asia (summarized in reference 128) in such countries as Saudi Arabia (119), Qatar (120), China (190), India (84, 161a), Malaysia (83), and the Philippines (106). In addition, Hib disease has been thoroughly characterized in some special populations such as Alaskan and Canadian Inuits (67, 181, 182), American Indians (146, 166), Australian Aborigines (69, 70), and the highlanders of Papua New Guinea (64, 101, 152). The conclusions of these studies agree that Hib diseases predominantly challenge developing regions and the poorest populations.

One of the few factors which may alleviate the gloomy calculations is the rather disputable evidence for a lower incidence in some countries in the Far East (128). For example, Japan has often been deemed a country with few Hib cases until an analysis of 824 cases of bacterial meningitis showed Hib to account for 35% of the cases (55). In an Indian series, Hib was responsible for 61% of cases (41), and in a study in Nepal, it was responsible for 65% (155). Another example was South Korea. For years it was stated that Hib meningitis was rare, until records from 14 hospitals in Seoul over a 10-year period (1986 to 1995) were reviewed (92). This study found that in children aged 3 months to 15 years, Hib was as common a cause of meningitis as the pneumococcus; both were responsible for 41% of cases, whereas meningococcus was found in only 8%. A number of patient series throughout the continent, often published in languages other than English, disclose the same phenomenon (128). The low incidence of Hib disease in non-Vietnamese populations in Hong Kong (98) (among Vietnamese refugees Hib disease is common) is often cited, but this information should not be taken as representative of the whole vast continent.

Studies on the incidence of Hib are regrettably rare from Asia. Those studies that exist (37, 38, 83, 98, 106, 119, 120, 171, 190) strongly suggest that the annual rates are not far from those once common in Europe—23 per 100,000 for Hib meningitis and 41 per 100,000 for all classical Hib diseases from age 0 to 4 years (127). Recently, the overall annual incidence in Asia of Hib meningitis plus classical manifestations in children aged 0 to 4 years was estimated to be around 25 and 40 per 100,000, respectively (128). In some countries, Hib meningitis seems to be clearly increasing in frequency, and this increase could not be ascribed to detection factors such as more active blood culturing or improved laboratory techniques (145). Community-based studies are urgently awaited.

In Latin America, information from 15 countries from Rio Grande to Tierra del Fuego and the Caribbean also demonstrated the importance of Hib disease (126): an overall incidence of Hib meningitis and the classical manifestations among children aged 0 to 4 years has been estimated at 35 and 60 per 100,000, respectively (126). Reliable information on the etiology of pneumonia based on lung tap was also obtained for Latin America (52, 110, 122, 142, 149); this method is also used in Africa and Oceania (115, 152, 180). *H. influenzae*, supposedly often Hib, turned out to be an essential pathogen in all these studies.

The numbers on Hib cases and deaths, as approximate as they might be, are so large that they should alert health authorities in many countries. There is no other nonepidemic and vaccine-preventable serious infection in which the incidence in a well-characterized risk group (children younger than 5 years) is as high as 71 per 100,000 or 370 per 100,000—depending on whether pneumonia is taken into account (Table 3)—which is overlooked by so many (Fig. 2 and 3). Less than 2% of Hib diseases worldwide are prevented, because some 80% of the 215 countries and territories reporting to the World Health Organization are not using Hib vaccines in their national immunization programs (168). Whether wide-scale protection would be feasible depends essentially on the ability of conjugates to prevent Hib pneumonia (161). The data from Chile and Gambia show that this is the case (96, 115).

The high cost of conjugates is a major obstacle, which could be overcome in four ways. First, the number of doses could be lowered. Instead of four total doses, several European countries use only two primary doses with a late booster (136) or

three consecutive doses (18), and they have reported excellent results (Table 4). Since the third dose improves efficacy by only about 5% (176), dose reduction not only is possible but also improves the cost-benefit ratio (104). An innovative approach would be to begin vaccinations in neonates (95) or even before birth (114). This is a great advantage in circumstances in which all contacts with nonvaccinees should be used for immunization.

Second, the good immunogenicity of conjugates allows the use of smaller antigen doses than are used to date. Between 90 and 100% of Chilean infants vaccinated with one-half or only one-third the traditional dose of PRP-T or PRP-CRM_{197} conjugate responded almost as well as if they had received the full dose (97). No doubt this approach saves vaccine, but the real economic savings have yet to be shown, since only a rather modest part of all vaccination costs are due to the vaccine itself.

Third, Hib conjugates can be combined with existing routine vaccines, but this must be done stepwise to avoid problems in immunogenicity (47). Also, this approach would reduce costs, improve coverage, and ultimately speed the fight against Hib diseases. Mexico is an illustrative example of a large, populous, and poor country that has adopted a pentavalent vaccine with a Hib antigen in routine childhood immunizations. It seems that reduced immunogenicity of some conjugates in conjunction with acellular pertussis vaccine has no practical significance (47a).

Fourth, the vaccine cost should be adjusted better to the prevailing resources. Because Hib diseases are rampant (though not always realized as a problem), there is great marketing potential. The good news is that the price has declined to around $2 per dose for some bulk purchases (28a), which, sad to say, is still too much for the poorest countries. Brazil has recently signed a "strategic alliance" with a European manufacturer so that Hib vaccine, along with some others, will be produced locally and at lower cost (28a). Safe and efficacious Hib vaccines should no longer be the privilege of certain peoples: preventing 38,000 cases a year among more than 2 million (a meager 1.7%, perhaps less) is just the beginning.

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